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Name _____ Date _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Cech et al.

Filing Date: November 2, 1999

Serial No: 09/432,503

Docket: 015389-002611US; 018/063c

Title: REDUCING TISSUE DAMAGE DUE TO IMPAIRED REPLICATION USING A VECTOR EXPRESSING TELOMERASE REVERSE TRANSCRIPTASE

Art Unit: 1645

Examiner: J. Eric Angell, Ph.D.

SECOND DECLARATION UNDER 37 CFR § 1.132
BY CALVIN B. HARLEY, Ph.D.

Commissioner for Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, CALVIN HARLEY, do hereby declare as follows:

I am the Chief Scientific Officer at Geron Corporation, and co-inventor on this patent application. An earlier Declaration in my name was filed in this application in February of 2003, accompanied with a copy of my *curriculum vitae*. I have been conducting research on telomere biochemistry and cell biology for over 17 years.

I am familiar with this patent disclosure and the pending claims. I understand the Examiner has questioned how adenovirus expression vectors for human telomerase reverse transcriptase (TRT) could be used to extend replicative capacity of human cells *in vivo* for the benefit of the patient being treated.

Experimental evidence has shown that TRT increases replicative capacity in a wide spectrum of human cell types in culture, and while doing so, offsets the decline in functional capacity associated with cell aging. It is expected that increasing replicative capacity will be beneficial for treating clinical conditions that fail to resolve adequately or quickly due to impaired cell replication and concomitant loss of functional capacity. Conditions suitable for treatment by TRT gene therapy would be those that are accessible and amenable to the TRT expression vector selected for use.

Adenovirus vectors are well adapted for treating a wide range of different tissues *in vivo*, since they typically transduce cells by way of the broadly expressed *human coxsackievirus and adenovirus receptor* (the CAR receptor, Bergelson et al., J. Virol. 72:415-419, 1968). Administration to a human of an adenovirus vector encoding TRT would increase telomerase enzyme activity and improve replicative capacity of cells normally capable of proliferation. In clinical conditions where there is damage due to impaired cell replication, treatment with a TRT adenovirus expression vector could be used to increase the rate or extent of replication, or otherwise confer benefits to reduce damage to the tissue or promote healing.

The scientists at Geron have confirmed the utility of TRT gene therapy both *in vitro* and *in vivo*. We also have a program for developing small-molecule drugs to increase telomerase activity in cells (WO 2005/003430 and WO 2005/044179). Ultimately, the selection of clinical conditions for treatment with a TRT gene therapy vector or a small-molecule telomerase activator will depend in part on the nature of each condition, and the accessibility of the disease site.

Since cloning the TRT gene in 1997, there have been a significant number of publications on tissue culture and animal models as well as human epidemiological studies supporting our concept of telomerase induction or activation for degenerative conditions. In response to an invitation from the editors of the journal Current Molecular Medicine, I recently conducted a critical review of the use of telomerase specific agents in clinical care (C. Harley, Curr. Molec. Med. 5:29-38, 2005, a copy of which is enclosed with this Declaration). Table 1 (p. 207) lists cell types that have been shown to respond to telomerase gene transduction with improved replicative capacity. Table 2 (p. 208) lists five *in vivo* models in which TRT transduced cells have improved function. Table 3 (p 209) lists some of the disease conditions that would benefit from increasing telomerase enzyme activity.

At the present time, we believe that suitable tissue targets and clinical conditions for up-regulating telomerase activity include the following:

- *skin* – for example, in chronic wounds, topical treatment with a TRT vector or a telomerase activator should improve formation of granulation tissue, tissue repair, and complete closure of wounds.
- *hair cells* – for example, in hair loss, topical treatment with a TRT vector or a telomerase activator should help regenerate hair follicle growth and improve abundance and quality of hair.
- *hepatocytes* – for example, in cirrhosis, intravenous administration of a TRT vector or oral administration of a bioavailable telomerase activator should improve hepatocyte renewal and function, and hence help repair liver damage.
- *endothelial cells* – for example, in cardiovascular diseases, including small and large vessel disease in essentially any organ of the body, intravenous administration of a TRT vector, either locally or systemically, or oral administration of a bioavailable telomerase activator, should improve renewal and function of endothelial cells, and help repair damaged vasculature or allow new vessel formation or growth, and improve the function of affected organs.
- *RPE cells* – for example, in age-related macular degeneration (AMD), intra-ocular injection of a TRT vector or oral administration of a bioavailable telomerase activator should improve RPE cell renewal and function, and restore normal regulation of blood vessel growth (i.e., down-regulate angiogenesis associated with AMD) and hence improve eyesight.

- *cementoblasts, odontoblasts, osteoblasts, chondrocytes, stromal and mesenchymal stem cells* – for example in bone, connective tissue, and joint diseases, local or intravenous administration of a TRT vector or oral administration of a bioavailable telomerase activator should improve renewal and function of these and other types of connective tissue and bone cells, including the associated stem cells, and hence help repair joint and bone structure and function.
- *cardiomyocytes* – for example, in heart disease, local or systemic intravenous administration of a TRT vector or oral administration of a bioavailable telomerase activator should improve cardiomyocyte function and resistance to hypoxic stress and apoptosis, and hence help reduce damage to heart muscle associated with heart disease.
- *leukocytes* – for example, in immune disease such as HIV/AIDS and in infections in the elderly, intravenous administration of a TRT vector or oral administration of a bioavailable telomerase activator should improve leukocyte renewal and function, especially in CD8+ and CD4+ T effector and regulatory cells), and hence control or eliminate cells infected with foreign agents.

Advantages of using TRT vectors are expected to include the ability to induce telomerase activity in cells with no or low expression of endogenous TRT, and ongoing synthesis of TRT as the expression vector persists in the treated tissue.

I hereby declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

2006.03.09
Date

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